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Original article

Initial digital vasculitis in a large multicenter cohort of childhood-onset systemic lupus erythematosus

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ABSTRACT

Objectives: To assess clinical digital vasculitis (DV) as an initial manifestation of childhood-onset systemic lupus erythematosus (cSLE) within a large population.
Methods: Multicenter cross-sectional study including 852 cSLE patients (ACR criteria) followed in ten Pediatric Rheumatology centers in São Paulo State, Brazil.
Results: DV was observed in 25/852 (3%) cSLE patients. Periungual hemorrhage was diagnosed in 12 (48%), periungual infarction in 7 (28%), tip finger ulceration in 4 (16%), painful nodules in 1 (4%) and gangrene in 1 (4%). A poor outcome, with digital resorption, occurred in 5 (20%). Comparison of patients with and without DV revealed higher frequency of malar rash (80% vs. 53%, $p = 0.008$), discoid rash (16% vs. 4%, $p = 0.017$), photosensitivity (76% vs. 45%, $p = 0.002$) and other cutaneous vasculitides (80% vs. 19%, $p < 0.0001$), whereas the frequency of overall constitutional features (32% vs. 61%, $p = 0.003$), fever (32% vs. 56%, $p = 0.020$) and hepatomegaly (4% vs. 23%, $p = 0.026$) were lower in these patients. Frequency of female gender, severe multi-organ involvement, autoantibodies profile and low complement were alike in both groups ($p > 0.05$). SLEDAI-2K median, DV descriptor excluded, was significantly lower in patients with DV compared to those without this manifestation [10 (0–28) vs. 14 (0–58), $p = 0.004$]. Visceral vasculitis or death were not observed in this cSLE cohort. The frequency of cyclophosphamide use (0% vs. 18%, $p = 0.014$) was significantly lower in the DV group.

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Conclusion: Our large multicenter study identified clinical DV as one of the rare initial manifestation of active cSLE associated with a mild multisystemic disease, in spite of digital resorption in some of these patients.

Vasculite digital inicial em uma grande coorte multicêntrica de pacientes com lúpus eritematoso sistêmico de início na infância

Palavras-chave:
Vasculite digital
Lúpus eritematoso sistêmico de início na infância
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RESUMO

Objetivos: Avaliar a vasculite digital (VD) clínica como uma manifestação inicial do lúpus eritematoso sistêmico de início na infância (LESi) em uma grande população.
Métodos: Estudo transversal multicêntrico que incluiu 852 pacientes com LESi (critérios do ACR), acompanhados em dez centros de reumatologia pediátrica do Estado de São Paulo.
Resultados: Observou-se VD em 25/852 (3%) pacientes com LESi. Diagnosticaram-se hemorragia periungueal em 12 (48%), infarto periungueal em sete (28%), úlcera de ponta de dígito em quatro (16%), nódulos dolorosos em um (4%) e gangrena em um (4%). Um desfecho ruim, com reabsorção digital, ocorreu em cinco (20%) pacientes. A comparação entre pacientes com e sem VD revelou maior frequência de erupção malar (80% vs. 53%, p = 0,008), erupção discoide (16% vs. 4%, p = 0,017), fotossensibilidade (76% vs. 45% p = 0,002) e outras vasculites cutâneas (80% vs. 19%, p < 0,0001), enquanto a frequência de características constitucionais totais (32% vs. 61%, p = 0,003), febre (32% vs. 56% p = 0,020) e hepatomegalia (4% vs. 23%, p = 0,026) foram menores nesses pacientes. A frequência do gênero feminino, o envolvimento grave de múltiplos órgãos, perfil de autoanticorpos e baixo complemento foram semelhantes nos dois grupos (p > 0,05). A mediana no Sledai-2 K, exclusive o descritor de VD, foi significativamente menor nos pacientes com VD em comparação com aqueles sem essa manifestação [10 (0 a 28) vs. 14 (0 a 58), p = 0,004]. Não foram observadas vasculite visceral nem morte nessa coorte de pacientes com LESi. A frequência de uso de ciclofosfamida (0% vs. 18%, p = 0,014) foi significativamente menor no grupo VD.
Conclusão: Este grande estudo multicêntrico identificou a VD clínica como uma rara manifestação inicial do LESi ativo, associada a doença multissistêmica leve, apesar da ocorrência de reabsorção digital em alguns desses pacientes.

Introduction

Systemic lupus erythematosus (SLE) is a multisystemic autoimmune chronic disease more common in adults (aSLE), with only 10–20% of cases beginning during childhood or adolescence.[1–3] Childhood-onset SLE (cSLE) is characterized by more severe and cumulative acute organ and system involvement comparing to aSLE. Mucocutaneous involvement is one of the most common manifestations and has been reported in up to 80% of children and adolescents at the time of diagnosis.[1,2]

Vascular inflammatory process is an important feature of SLE and affects a large subset of patients with skin manifestations at any time of disease course.[4–7] SLE clinical digital vasculitis (DV) includes painful ulceration and nodules may result in splinter hemorrhages and digital infarcts[1,8,9] and it may be present in 16–45% of aSLE patients.[5,7,8,10]

Data on cSLE patients are limited to case reports and small series.[1,9,11] There are no published data characterizing DV in a large population of childhood lupus patients.

Therefore, the objective of this study was to assess DV as an initial manifestation in a large multicenter study, evaluating the possible association with demographic and clinical features, laboratorial exams, treatment and outcomes in cSLE onset.

Methods

Study design and patients

This is a retrospective multicenter study including 1017 cSLE patients followed in ten Pediatric Rheumatology tertiary referral centers in São Paulo state, Brazil. One hundred and sixty-five patients were excluded due to: incomplete medical charts ($n = 96$), undifferentiated connective tissue disorder with 3 or fewer American College of Rheumatology (ACR) criteria for SLE[12] ($n = 43$), isolated cutaneous lupus erythematosus ($n = 11$), neonatal lupus erythematosus ($n = 8$), drug-induced lupus ($n = 5$) and other autoimmune diseases ($n = 2$). Thus, the study group comprised 852 cSLE patients; all fulfilled the ACR

criteria[12] and presented disease onset before 18 years old[13] with a current age up to 25 years. Committee for Research Ethics of each center approved the study.

An investigator meeting was held for this study to define the protocol, including definitions of clinical, laboratory and treatment parameters and disease activity and damage score. All investigators used the same specific database.

Patient's medical charts were meticulously revised according to a standardized protocol for demographic data, DV characteristics, other clinical features, laboratorial findings, therapeutic data and DV outcome (digital resorption, visceral vasculitis and death). Clinical DV was defined as ulceration, gangrene, tender finger nodules, periungual infarction or splinter hemorrhages of the digits according to SLE Disease Activity Index 2000 score (SLEDAI-2K).[14]

Demographic data, clinical evaluation, disease activity, disease damage and drug therapy

Demographic data included gender, ethnicity and age at cSLE onset. Descriptors and definitions of SLEDAI-2K were used to score disease activity.[14] Other SLE clinical manifestations included: fever (axillary temperature higher than 37.8 °C), weight loss > 2 kg, lymphadenopathy (peripheral lymph node enlargement > 1.0 cm), hepatomegaly [based on physical exam with liver edge ≥2 cm below the right costal margin or imaging (ultrasound or computer tomography when available)] and splenomegaly [based on physical exam with palpable spleen or imaging (ultrasound or computer tomography when available)].[15] Neuropsychiatric lupus included 19 syndromes according to ACR classification criteria.[16] Antiphospholipid syndrome was diagnosed according to the preliminary criteria for the classification of pediatric antiphospholipid syndrome.[17] High blood pressure was defined as systolic and/or diastolic blood pressures ≥95th percentile for gender, age and height on ≥3 occasions.[18] Acute kidney injury was determined by sudden increase in serum creatinine above 2 mg/dl[19] or by modified RIFLE (Risk, Injury, Failure, Loss of kidney function and End-stage kidney disease) criteria.[20] Chronic renal disease was defined as structural or functional abnormalities of the kidney for ≥3 months (with or without decreased glomerular filtration rate) or glomerular filtration rate < 60 ml/min/1.73 m^2 for ≥3 months.[21]

Laboratorial assessment was comprised of retrospective analysis of erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), complete blood cell count, serum urea and creatinine, urinalysis and 24-h urine protein excretion. Complement levels (CH50, C3 and C4) were assessed by immunodiffusion, turbidimetric immunoassay or immunonephelometry. Antinuclear antibodies (ANA) were tested by indirect immunofluorescence; anti-double-stranded DNA (anti-dsDNA) by indirect immunofluorescence or Enzyme Linked Immuno Sorbent Assay (ELISA) and anticardiolipin (aCL) IgG and IgM by ELISA were carried out at each center. The cutoff values given by the kit manufacturer were used to define normal or abnormal findings. Lupus anticoagulant was detected according to the guidelines of the International Society on Thrombosis and Hemostasis.[22]

Table 1 – Clinical characteristics and outcome of digital vasculitis (DV) in 852 cSLE patients at diagnosis.

DV characteristics	cSLE $n = 25$ (%)
DV duration, days	56 (10–933)
Number of affected fingers or toes	5 (1–20)
Periungual hemorrhage	12 (48)
Periungual infarct	7 (28)
Ulceration	4 (16)
Gangrene	1 (4)
Painful nodules	1 (4)
Outcome	
Digital resorption	5 (20)
Visceral vasculitis	0 (0)

cSLE, childhood-onset systemic lupus erythematosus.
Results are presented as median (range) and *n* (%).

Drug treatment data (prednisone, intravenous methylprednisolone, chloroquine diphosphate, hydroxychloroquine sulfate, methotrexate, azathioprine, cyclosporine, mycophenolate mofetil, intravenous cyclophosphamide, intravenous immunoglobulin, rituximab and plasmapheresis) were also recorded.

Patients were divided in two groups at the cSLE diagnosis for the assessment of cSLE manifestations, laboratory exams and treatment: patients with DV and without DV.

Statistical analysis

All statistical analyses were performed with the Statistical Package for the Social Sciences (SPSS), version 13.0. Results were given as numbers (percentage) for categorical variables, median (range) or mean ± standard deviation (SD) for continuous variables. Comparisons between categorical variables were assessed by Pearson χ-square or Fisher's exact test and continuous variables comparisons were compared by Mann–Whitney test or *t* test. The significance levels of the independent variable were set at 5% ($p < 0.05$).

Results

DV was observed in 25/852 (2.9%) cSLE patients at diagnosis. Periungual hemorrhage on the fingers was found in 12 (48%) cSLE patients, periungual infarct in 7 (28%), digital ulceration in 4 (16%), digital gangrene in 1 (4%) and digital painful nodules in 1 (4%) patient. The median of affected fingers or toes was five (1–20). The features of DV and its outcome in 25/852 cSLE are shown in Table 1.

Further comparisons of demographic data and current clinical manifestations in 852 cSLE patients with and without DV at diagnosis are illustrated in Table 2. The frequency of constitutional features (32% vs. 61%, $p = 0.003$), fever (32% vs. 56%, $p = 0.020$), hepatomegaly (4% vs. 23%, $p = 0.026$) and arterial hypertension (0% vs. 25%, $p = 0.001$) were significantly lower in cSLE patients with DV compared to those without this manifestation. On the other hand, mucocutaneous involvement (100% vs. 79%, $p = 0.005$), rash (80% vs. 53%, $p = 0.008$), discoid lupus (16% vs. 4%, $p = 0.017$), photosensitivity (76% vs.

Table 2 – Demographic data and current clinical manifestations in 852 childhood-onset systemic lupus erythematosus (cSLE) patients grouped according to digital vasculitis (DV) at the diagnosis.

Variables	With DV (*n* = 25)	Without DV (*n* = 827)	*p*
Demographic data			
Female gender, n = 852	22/25 (88)	710/827 (86)	1.000
Caucasian, n = 830	8/24 (33)	230/806 (29)	0.609
Age at cSLE onset, years, n = 852/852	13 (4.25–17)	11.8 (0.25–17.8)	0.067
Clinical manifestations			
Constitutional features, n = 843	8/25 (32)	501/818 (61)	0.003
Fever, *n* = 837	8/25 (32)	451/812 (56)	0.020
Weight loss > 2 kg, *n* = 822	7/25 (28)	251/797 (32)	0.385
Reticuloendothelial system involvement, n = 831	5/25 (20)	267/806 (33)	0.199
Lymphadenopathy, *n* = 825	4/25 (16)	164/800 (21)	0.801
Hepatomegaly, *n* = 831	1/25 (4)	181/806 (23)	0.026
Splenomegaly, *n* = 830	0/25 (0)	76/805 (9)	0.157
Mucocutaneous involvement, n = 848	25/25 (100)	651/823 (79)	0.005
Rash, *n* = 842	20/25 (80)	434/817 (53)	0.008
Discoid lupus, *n* = 844	4/25 (16)	31/819 (4)	0.017
Photosensitivity, *n* = 844	19/25 (76)	367/819 (45)	0.002
Mucosal ulcer, *n* = 845	8/25 (32)	276/820 (34)	0.863
Alopecia, *n* = 843	11/25 (25)	251/818 (31)	0.156
Other skin vasculitis lesions, *n* = 844	20/25 (80)	152/819 (19)	<0.0001
Musculoskeletal involvement, n = 846	18/25 (72)	561/821 (68)	0.697
Myositis, *n* = 843	2/25 (8)	32/818 (4)	0.267
Arthritis, *n* = 850	17/25 (68)	555/825 (67)	0.939
Serositis, n = 847	5/25 (20)	233/822 (28)	0.499
Pleuritis, *n* = 846	1/25 (4)	148/821 (18)	0.104
Pericarditis, *n* = 846	5/25 (20)	163/821 (20)	1.000
Neuropsychiatric involvement, n = 847	2/25 (8)	202/822 (25)	0.059
Peripheral nervous system involvement, *n* = 847	0/25 (0)	7/818 (1)	1.000
Central nervous system involvement, *n* = 843	2/25 (8)	198/822 (24)	0.090
Nephritis, n = 836	8/25 (32)	406/811 (50)	0.075
Hematuria, *n* = 825	9/25 (36)	358/800 (45)	0.386
Pyuria, *n* = 821	4/25 (16)	269/796 (34)	0.083
Urinary cast, *n* = 822	3/25 (12)	171/797 (22)	0.326
Proteinuria > 0.5 g/day, *n* = 804	7/25 (28)	368/779 (47)	0.058
Anti-phospholipid syndrome, n = 785	0/25 (0)	15/760 (2)	1.000
Ocular involvement, n = 841	1/25 (4)	13/816 (2)	0.347
Other			
Arterial hypertension, *n* = 840	0/25 (0)	202/815 (25)	0.001
Acute renal failure, *n* = 839	1/25 (4)	98/814 (12)	0.346
Chronic renal failure, *n* = 835	0/25 (0)	18/810 (2)	1.000

Results are presented in *n* (%) and median (range).

45%, $p = 0.002$) and other skin vasculitis lesions (80% vs. 19%, $p < 0.0001$) were significantly higher in cSLE patients with DV compared to those without this cutaneous involvement. A tendency of lower frequency of neuropsychiatric ($p = 0.059$) and renal involvement ($p = 0.075$) was observed in patients with DV (Table 2). None of the patients with DV had antiphospholipid syndrome or thrombotic thrombocytopenic purpura.

Disease activity and laboratory tests of 852 cSLE patients are shown in Table 3. The median of SLEDAI-2K including the DV score item [20 (8–36) vs. 14 (0–58), $p = 0.014$] was significantly higher in DV patients compared to patients without this complication. On the other hand, when calculating the median of SLEDAI-2K excluding DV descriptor [10 (0–28) vs. 14 (0–58), $p = 0.004$], it was lower in the group with DV, scored mainly by mucocutaneous involvement [rash (80%) and mucosal ulcers (32%)]. In spite of that, all patients with DV had SLEDAI-2K > 8. The laboratory tests comparison was similar in both groups ($p > 0.05$, Table 3).

Therapy in cSLE patients with and without DV at the time of diagnosis is shown in Table 4. The frequency of cyclophosphamide use (0% vs. 18%, $p = 0.014$) was significantly lower in patients with DV compared to those without this manifestation. Frequency of other medications use was similar in both groups ($p > 0.05$, Table 4). No cSLE patient was treated with intravenous immunoglobulin, rituximab or plasmapheresis at diagnosis.

Regarding outcome, digital resorption was evidenced in 5/25 (20%). Visceral vasculitis or death was not observed in cSLE patients with DV, with no statistical significance compared to the patients with no DV.

Discussion

Our large multicenter cohort was the first characterizing DV as one of the rare initial manifestations of cSLE patients, mainly associated with other mucocutaneous involvement.

Table 3 – Current disease activity and laboratory tests in 852 childhood-onset systemic lupus erythematosus (cSLE) patients grouped according to digital vasculitis (DV) at diagnosis.

Variables	With DV ($n=25$)	Without DV ($n=827$)	p
Current disease activity/damage scores			
SLEDAI-2K with DV score, $n=789/852$	20 (8–36)	14 (0–58)	0.014
SLEDAI-2K without DV score, $n=789/852$	10 (0–28)	14 (0–58)	0.004
SLEDAI-2K ≥ 8, $n=789/852$	25 (100)	743 (90)	0.062
Laboratory tests			
ESR mm/1st/hour, $n=717/852$	44 (10–130)	50 (1–160)	0.601
CRP mg/dL, $n=454/852$	1.85 (0–47)	3 (0–413)	0.531
Autoimmune hemolytic anemia, $n=830$	3/25 (12)	170/805 (21)	0.328
Leucopenia $<4000\,mm^{-3}$, $n=836$	5/25 (20)	222/811 (27)	0.500
Lymphopenia $<1500\,mm^{-3}$, $n=834$	9/25 (36)	349/809 (43)	0.157
Thrombocytopenia, $<100{,}000\,mm^{-3}$, $n=834$	1/25 (4)	128/809 (16)	0.540
Low C3, C4 and/or CH50, $n=727$	21/23 (91)	511/704 (73)	0.054
Anti-dsDNA antibody, $n=801$	15/25 (60)	542/776 (70)	0.292
Lupus anticoagulant, $n=415$	1/18 (6)	64/397 (16)	0.330
Anticardiolipin IgM antibody, $n=498$	1/19 (5)	110/479 (23)	0.090
Anticardiolipin IgG antibody, $n=496$	3/18 (17)	130/478 (27)	0.270

SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein. Results are presented in n (%) and median (range).

Table 4 – Therapy in 852 childhood-onset systemic lupus erythematosus (cSLE) patients grouped according to digital vasculitis (DV) at diagnosis.

Variables	With DV ($n=25$)	Without DV ($n=827$)	p
Nonsteroidal anti-inflammatory, $n=836$	2/25 (8)	115/811 (14)	0.380
Glucocorticosteroids			
Prednisone, $n=836$	24/25 (96)	757/811 (93)	1.000
Current dose, mg/day, $n=762/852$	40 (10–75)	40 (3–180)	0.421
mg/kg/day, $n=728/852$	1.0 (0.2–2)	1.0 (0.1–4)	0.438
Intravenous methylprednisolone, $n=821$	10/25 (40)	348/796 (44)	0.712
Antimalarial drugs, $n=838$	18/25 (72)	444/813 (55)	0.085
Immunosuppressive agents			
Azathioprine, $n=839$	6/25 (24)	100/814 (12)	0.082
Cyclosporine, $n=839$	0/25 (0)	8/814 (1)	1.000
Methotrexate, $n=840$	3/25 (12)	33/815 (4)	0.087
Mycophenolate mofetil, $n=838$	1/25 (4)	8/813 (1)	0.240
Cyclophosphamide, $n=841$	0/25 (0)	144/816 (18)	0.014
Others			
Intravenous immunoglobulin, $n=845$	0/25 (0)	28/820 (3)	1.000
Rituximab, $n=843$	0/25 (0)	0/818 (0)	–
Plasmapheresis, $n=841$	0/25 (0)	11/816 (1)	1.000

Results are presented in n (%).

The advantage of including a large cSLE population selected in tertiary referral centers allowed a better evaluation of this rare vasculitic manifestation. The use of a standardized combined database, with proper DV definition, minimized possible bias. However, the main limitation of this study was the retrospective design and possible missing data, as well as no biopsy or angiographic evidence of vasculitis in any of our patients. It was not possible to examine nailfold capillaroscopy because it was not a routine procedure in all participant Pediatric Rheumatology centers. This exam could be useful as a tool for disease activity assessment related to small vessels involvement in cases with DV.[23,24]

Vascular skin injury is an important characteristic of SLE and affects the majority of patients during the whole disease course and it was reported in association with lupus flares or thrombosis.[8–10] We confirmed the possible association with active disease and less probable association with antiphospholipid syndrome due to the absence of antiphospholipid antibodies in DV cases. Of note, SLEDAI-2K evaluation revealed a predominance of mucocutaneous involvement and lower frequency of major organ involvements (neuropsychiatric and renal) reinforcing the concept that DV is associated with mild systemic disease activity and more active skin disease. DV descriptor has weight of 8 and consequently contributes with high values of SLEDAI-2K score, despite of the mild disease that this manifestation represented in our patients.[9]

Despite the fact that skin vasculitis is a common lupus manifestation at diagnosis of aSLE and cSLE patients, clin-

ical DV was rarely reported in adults[11,25] and cSLE.[1,8,9] In a cross-sectional study with 168 aSLE patients, DV appeared in 16% of the patients associated with constitutional symptoms, mucocutaneous and hematological manifestations.[7] In another study reporting 670 aSLE cases, 11% presented digits ulceration and/or ischemic lesions.[25] We observed from our results that although the frequency of DV at cSLE diagnosis is very low, it is in fact associated with permanent damage in 1/5 of the patients.

DV was not associated with any lupus specific antibody. Only a few patients had antiphospholipid antibodies, characterizing a distinct profile from those with more severe organ involvement.[26–28] Although it is not possible to exclude antiphospholipid syndrome in these patients, the absence of clinical criteria makes this diagnosis very unlikely. The only clinical feature was the digital thrombotic vascular damage that may have had a similar clinical aspect to lupus vasculitis.[4–7] Further studies regarding this association are necessary.

The majority of SLE patients with small vessel lesions had clinical DV characterized by erythematous punctuate lesions on the fingers,[7] as observed in our study. This feature is different from those cSLE patients with visceral medium vessel vasculitis associated with increased morbidity and mortality due to involvement of cerebrovascular, gastrointestinal, renal, cardiovascular and pulmonary involvements.[29–32] Intravenous cyclophosphamide treatment was less frequent reinforcing the concept of milder systemic activity of the cases. Furthermore, concomitant visceral and cutaneous vasculitis is rare in aSLE (2%),[33] emphasizing the importance of distinguishing between these two subtypes of vasculitis.

In conclusion, our large multicenter study identified clinical DV as a rare initial manifestation of active cSLE associated with mild multisystemic disease in spite of accrued damage with digital resorption in some of these patients.

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Conflicts of interest

The authors declare no conflicts of interest.

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